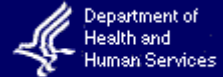


EXHIBIT H



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Information for Healthcare Professionals Suicidality and Antiepileptic Drugs

FDA ALERT [1/31/2008]: The FDA has analyzed reports of suicidality (suicidal behavior or ideation) from placebo-controlled clinical studies of eleven drugs used to treat epilepsy as well as psychiatric disorders, and other conditions. These drugs are commonly referred to as antiepileptic drugs (see the list below). In the FDA's analysis, patients receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation (0.43%) compared to patients receiving placebo (0.22%). The increased risk of suicidal behavior and suicidal ideation was observed as early as one week after starting the antiepileptic drug and continued through 24 weeks. The results were generally consistent among the eleven drugs. Patients who were treated for epilepsy, psychiatric disorders, and other conditions were all at increased risk for suicidality when compared to placebo, and there did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed. The relative risk for suicidality was higher in the patients with epilepsy compared to patients who were given one of the drugs in the class for psychiatric or other conditions.

All patients who are currently taking or starting on any antiepileptic drug should be closely monitored for notable changes in behavior that could indicate the emergence or worsening of suicidal thoughts or behavior or depression.

This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA intends to update this document when additional information or analyses become available.

Adverse reactions or quality problems experienced with the use of this product may be reported to the FDA's MedWatch Adverse Event Reporting program; see addresses below.

Considerations for Physicians and Other Health Care Professionals

Data from 199 placebo-controlled clinical studies covering eleven different antiepileptic drugs were reviewed and analyzed for reports of suicidal behavior (completed suicides, suicide attempts and preparatory acts) and suicidal ideation. The studies examined the effectiveness of

the drugs in epilepsy, psychiatric disorders (e.g., bipolar disorder, depression and anxiety) and other conditions (e.g., migraine and neuropathic pain syndromes). The analysis included a total of 43,892 patients ages five and older (27,863 in drug treatment groups and 16,029 in placebo groups).

There was a statistically significant increased risk of suicidal behavior and suicidal ideation in the patients randomized to receive an antiepileptic drug compared to patients who received a placebo. The estimated overall risk was about twice that of the placebo group. There were an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo groups.

Four of the patients who were taking one of the antiepileptic drugs committed suicide, whereas none of the patients in the placebo group did. The increased risk of suicidal behavior and suicidal ideation was observed at one week after starting the drug and continued to at least 24 weeks. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be reliably assessed.

FDA will be working with manufacturers of marketed antiepileptic drugs to include this new information in the labeling for these products. FDA is also planning to discuss these data at an upcoming advisory committee meeting.

All patients treated with antiepileptic drugs should be monitored for suicidality and other unusual changes in behavior. Symptoms such as anxiety, agitation, hostility, mania and hypomania may be precursors to emerging suicidality.

Healthcare professionals who prescribe antiepileptic drugs should:

- Balance the risk for suicidality with the clinical need for the drug
- Be aware of the possibility of the emergence or worsening of depression, suicidality, or any unusual changes in behavior;
- Inform patients, their families, and caregivers of the potential for an increase in the risk of suicidality so they are aware and able to notify their healthcare provider of any unusual behavioral changes.

Information for patients, family members, and caregivers:

- Taking antiepileptic medicines may increase the risk of having suicidal thoughts or actions;
- Do not make any changes to the medication regimen without first talking with the responsible healthcare professional;
- Pay close attention to any day-to-day changes in mood, behavior and actions. These changes can happen very quickly so it is important to be mindful of any sudden differences.
- Be aware of common warning signs that might be a signal for risk of suicide. Some of these are:
 - Talking or thinking about wanting to hurt yourself or end your life
 - Withdrawing from friends and family
 - Becoming depressed or having your depression get worse
 - Becoming preoccupied with death and dying
 - Giving away prized possessions

If these or any new and worrisome behaviors occur, contact the responsible healthcare professional immediately.

Background and Data Summary

After preliminary analyses of data from several drugs in this class suggested an increased risk of suicidality, in March 2005, FDA requested data from manufacturers of marketed antiepileptic drugs for which there were adequately designed controlled clinical trials in order to review the possible association between these drugs and suicidality events. In an effort to obtain the most complete and accurate data for this review, requests for additional information and clarification were sent to the manufacturers in 2006 and 2007. The analyses performed were similar to those performed by FDA for antidepressant drugs in the last several years.

One-hundred ninety nine placebo-controlled clinical studies covering eleven different drugs were included in the primary analysis. The conditions studied in these clinical trials included epilepsy, selected psychiatric illnesses, and other indications, including migraine and neuropathic pain syndromes. The analysis included 27,863 patients in drug treatment groups and 16,029 patients in placebo groups. Patients included in the analysis were five years of age or older. The individual sponsors of the drugs were responsible for identifying suicidal behavior and suicidal ideation events in their databases based on the instructions provided by FDA.

There were 4 completed suicides among patients in drug treatment groups and none among the patients in placebo groups. Overall, 0.43% of the patients in drug treatment groups experienced suicidal behavior or ideation versus 0.22% of the patients in placebo groups, corresponding to an estimated 2.1 per 1000 (95% CI: 0.7, 4.2) more patients in the drug treatment groups who experienced suicidal behavior or ideation than in the placebo treatment groups (See Table). In this analysis, the relative risk for suicidal thoughts or behavior was higher for patients with epilepsy compared to those patients with psychiatric or other disorders (See Table). The higher risk for suicidal behavior or suicidal ideation was observed at one week after starting a drug and continued to at least 24 weeks. The results were generally consistent among the drugs and were seen in all demographic subgroups. Specifically, there was no clear pattern of risk across age groups.

Relative Risk and Risk Difference for Suicidality According to Trial

Indication

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.5	3.6	2.5
Psychiatric	5.2	8.3	1.6	3.1
Other	0.8	2.0	2.3	1.1
Total	2.2	4.3	2.0	2.1

The following is a list of antiepileptic drugs* included in the analyses:

- [Carbamazepine](#) (marketed as Carbatrol, Equetro, Tegretol, Tegretol XR)
- Felbamate (marketed as Felbatol)
- [Gabapentin](#) (marketed as Neurontin)
- [Lamotrigine](#) (marketed as Lamictal)
- [Levetiracetam](#) (marketed as Keppra)
 - [Patient Information Sheet](#)
- [Oxcarbazepine](#) (marketed as Trileptal)
- [Pregabalin](#) (marketed as Lyrica)
- [Tiagabine](#) (marketed as Gabitril)
- [Topiramate](#) (marketed as Topamax)
- [Valproate](#) (marketed as Depakote, Depakote ER, Depakene, Depacon)
- [Zonisamide](#) (marketed as Zonegran)

* Some of these drugs are also available in generic form.

Although the drugs listed above were the ones included in the analysis, FDA expects that the increased risk of suicidality is shared by all AEDs and anticipates that the class labeling changes will be applied broadly.

Adverse reactions or quality problems experienced with the use of this Product may be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax.

- **Online:** www.fda.gov/medwatch/report.htm
- **Regular Mail:** use postage-paid FDA form 3500 available at: www.fda.gov/MedWatch/getforms.htm.
- Mail to MedWatch 5600 Fishers Lane, Rockville, MD 20852-9787
- **Fax:** 1-800-FDA-0178

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